REMARKS

Claims 50, 52, 55-63, 65-68, 70, 72-78, and 84 are pending in the application. Claims 1-49, 51, 53, 54, 64, 69, 71, and 79-83 have been cancelled without prejudice or disclaimer. Claim 50 is amended. Following entry of the amendment, claims 50, 52, 55-63, 65-68, 70, 72-78, and 84 are pending in the application.

Rejection of claims under 35 U.S.C. §102 for anticipation

Claims 50, 55-63, 65-68, 70, and 84, which are directed to methods of inducing new blood vessel formation, are rejected under 35 U.S.C. §102 as allegedly anticipated by U.S. Patent Nos. 5,941,868 ("Kaplan") and 5,332,671 ("Ferrara"). For brevity, the rejections will be considered together. Additionally, because claims 55-63, 65-68, 70, and 84 depend directly or indirectly from independent claim 50, claims 55-63, 65-68, 70, and 84 also contain the features of claim 50.

The Office Action, at the bottom of page 5 alleges that "the claim [i.e., claim 50] to encompass the use of an effective fragment of VEGF, an effective fragment of GM-CSF or effective fragments of both VEGF and GM-CSF." Applicants respectfully disagree with the Office's statement. However, without in any way acquiescing to the rejection and in order to expedite prosecution, claim 50 has been amended to recite "a method for inducing new blood vessels in a mammal having chronic or acute ischemia ... [that] comprises administering to the mammal an effective amount of a vascular endothelial growth factor (VEGF), or an effective fragment thereof, and a granulocyte-macrophage colony stimulating factor (GM-CSF), or an effective fragment thereof." Thus, the claim requires administration of both a VEGF and GM-CSF, including effective fragments thereof.

Neither Kaplan nor Ferrara anticipate claim 50, because neither reference teaches or suggests administering GM-CSF in combination with VEGF. As the Office Action at page 8 states, "However, neither Kaplan et al. nor Ferrara et al. teach the use of both VEGF and GM-CSF in a method for inducing new blood vessels in a mammal having chronic or acute ischemia." By the Office's admission, neither Kaplan nor Ferrara teaches each and every element of the claim, as is required for a proper anticipation rejection. Therefore applicants request reconsideration and withdrawal of the rejections against claims 50, 55-63, 65-68, 70, and 84 under 35 U.S.C. §102(e) in view of Kaplan and under 35 U.S.C. §102(b) in view of Ferrara.

Rejection of claims under 35 U.S.C. §103 for obviousness

Claims 50, 52, 55-63, 65-68, 70, 72-73, 75, and 84 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over either Kaplan or Ferrara in view of Bussolino et al. (J. Clin. Invest. 87: 986-995, 1991) ("Bussolino"). Applicants respectfully disagree and traverse the rejection.

The claims are directed to a method of inducing formation of new blood vessels in a mammal having chronic or acute ischemia comprising the co-administration of **VEGF and GM-CSF**. In order to make out a *prima facie* showing of obviousness, the Examiner must establish that there is some motivation in one or the other of the cited references or in the state of the art at the time the invention was made to combine the references, the combination of references must teach or suggest each and every element of the claimed invention, and there must be some reasonable expectation of success in making and using the invention (M.P.E.P. §2143)..

The Office Action states that Kaplan teaches methods for promoting angiogenesis in tissue surrounding a body lumen with exemplary angiogenic factors including VEGF, bFGF, aFGF, EGF, PDGF, and fragments and combinations thereof. The Office Action also states that Ferrara teaches a method for treating trauma affecting the vascular endothelium by administering VEGF optionally with other novel or conventional therapies including treatment with growth factors. Applicants respectfully disagree.

As indicated in the above response to the rejections under 35 U.S.C. §102, the primary references do not teach the particular combination of VEGF and GM-CSF. This fact is also acknowledged at page 8 of the Office Action, which states:

> However, neither Kaplan et al. nor Ferrara et al teach the use of both VEGF and GM-CSF in a method for inducing new blood vessels in a mammal having chronic or acute ischemia

In other words, the deficiency of either Kaplan or Ferrara is that neither reference teaches or suggests **GM-CSF** and/or **G-CSF**.

I. There is no motivation in Bussolino, Kaplan, or Ferrara to combine the references.

The Office has cited Bussolino as an alleged remedy of the deficiency of Kaplan and/or Ferrara. However, Applicants respectfully submit that there is no motivation to combine Bussolino with either Kaplan or Ferrara to arrive at the claimed invention. Implicit in the

Office's rejection is the assumption that certain cytokines are fully functionally interchangeable with each other, e.g., VEGF and bFGF; **GM-CSF** and **G-CSF**. Regarding VEGF and bFGF, none of Kaplan, Ferrara, or Bussolino teaches that VEGF and bFGF are completely functionally equivalent. Even though Bussolino teaches the combination of **bFGF and G-CSF**, absent an express teaching that VEGF and bFGF are fully interchangeable, there is no motivation to combine **VEGF and G-CSF**.

Likewise, Applicants submit that the cytokines **GM-CSF** and **G-CSF** are also not completely functionally interchangeable. In support of this statement, results Bussolino obtained for **G-CSF** could not be predictably extended to **GM-CSF** (this point is elaborated in **Section II**). Therefore, even though Bussolino teaches the combination of **bFGF and G-CSF**, there is no motivation in the cited references to combine **VEGF and GM-CSF**, as claimed, let alone **VEGF and G-CSF**, as above.

II. Bussolino teaches that the *in vitro* HUVEC assay is not reliably predictive of *in vivo* angiogenic activity for combinations of cytokines.

The Office Action states that Bussolino demonstrates that **GM-CSF** and **G-CSF** are capable of inducing endothelial cells to proliferate and migrate *in vitro*, repair wounded monolayers, and act synergistically with bFGF in a corneal model of angiogenesis. Applicants respectfully disagree. Bussolino shows that **G-CSF** (but not **GM-CSF**) acts with bFGF in a corneal model of angiogenesis (Figure 6, p. 994, left column, 1st paragraph). Bussolino is silent regarding the effectiveness of **GM-CSF** in a corneal model of angiogenesis.

Regarding the relationship between obviousness of a combination and the predictability of results, MPEP § 2143.01(III) states:

> The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1396 (2007)("If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.").

As indicated in Applicants' previous response of May 23, 2008, the data in Bussolino would not suggest a reliance on the reference regarding the activity of **G-CSF** with bFGF, let alone the activity of **GM-CSF** with bFGF. At page 994, in the right hand column, Bussolino states:

> The cooperative angiogenic activity of **G-CSF and bFGF** was evident in terms of response intensity (number of capillaries, number of positive implants, time to reach the pellets). This initial observation needs to be extended. **However, the cooperative effect of G-CSF and bFGF in inducing in vivo angiogenesis was somewhat *surprising* and intriguing.** In fact, in vitro, in spite efforts involving different experimental designs only one of which is shown here (see Results), **we have found *no indication of a synergistic action* of these two cytokines on HUVEC proliferation and migration. *At best, an additive effect was observed.*** In vivo angiogenesis occurs as the endpoint of complex interactions between many events involving remodeling of the extracellular matrix and the release of several "factors" (12, 50). **This apparent *paradox* of a combination of cytokines acting directly on endothelial cells, showing a cooperative effect in vivo, but not in vitro, adds to the list of factors or conditions for which in vitro modulation of proliferation and migration is not necessarily predictive of in vivo effects on angiogenesis.** (emphasis added)

Bussolino teaches that the observations regarding the effect of **G-CSF** and bFGF in inducing in vivo angiogenesis were unexpected (i.e., ***"surprising"***), given that there was ***"no indication of a synergistic action* of G-CSF and bFGF on HUVEC proliferation and migration**. From these results, Bussolino, one of skill in the art, concludes that "**in vitro modulation of proliferation and migration is not necessarily predictive of in vivo effects on angiogenesis**." In other words, Bussolino did not find the results of the *in vitro* HUVEC assay a predictable indicator of the activity of **G-CSF and bFGF** in inducing *in vivo* angiogenesis (i.e., ***"this apparent paradox"***), and cautions against extending the results of the *in vitro* HUVEC assay to in vivo angiogenic activity.

However, the claims are directed to methods comprising a combination of **GM-CSF** and bFGF. Bussolino only measured the activity of **GM-CSF** and bFGF in the *in vitro* HUVEC assays, and did not perform *in vivo* rabbit corneal assays using **GM-CSF** and bFGF. Because Bussolino only measured the activity of **GM-CSF** and bFGF *in vitro* and because Bussolino states that, for combinations of cytokines, *in vitro* proliferation and migration is not predictive of *in vivo* angiogenesic activity, one of skill in the art would not conclude that **GM-CSF** and bFGF have *in vivo* angiogenic activity based solely on the results obtained in the *in vitro* HUVEC assays for **GM-CSF** and bFGF.

Thus, the data resulted in a ***"paradox"*** rather than an understanding. That is, to determine if **GM-CSF** and bFGF induce angiogenesis *in vivo*, more experiments need to be done with **GM-CSF** and bFGF (e.g., rabbit corneal assay with **GM-CSF** and bFGF). Additionally, even though Bussolino describes observations for **G-CSF** and bFGF *in vivo*, these conclusions cannot be generalized to **GM-CSF** and bFGF *in vivo*. When Bussolino is taken as a whole (i.e., MPEP §2141.02 (VI)), per the author, the reference only provides an invitation to further experimentation rather than firm conclusions, regarding the combination of **GM-CSF** and bFGF. Given this unpredictability, one would not have a reasonable expectation of success in arriving at the claimed invention based on Bussolino in combination with either Kaplan or Ferrara.

III. Bussolino in combination with either Kaplan or Ferrara does not teach or suggest the claimed invention.

Applicants also respectfully submit that Bussolino does not remedy the deficiency of either Kaplan or Ferrara because Bussolino, when combined with either Kaplan or Ferrara, still does not teach or suggest the claimed invention. Once again, the claims are directed to a method comprising the co-administration of **VEGF and GM-CSF**. Kaplan and Ferrara teach *inter alia* VEGF and bFGF, but do not teach **GM-CSF** or **G-CSF.** Furthermore, Bussolino only provides an enabling disclosure for the combination of **bFGF and G-CSF**, which is not predictive of nor applicable to the combination of **VEGF and GM-CSF**, as described above. Therefore, the combination of references does not teach or suggest the claimed invention (i.e., the combination of **VEGF and GM-CSF**).

In sum, there is nothing in either of the cited references or in the state of the art at the time the invention was made that provides one of ordinary skill in the art with the motivation to combine the references in the manner proffered by the Examiner (**Section I**). Even so, none of the references teaches or suggests the predictability of the combination of **VEGF and GM-CSF** for increasing angiogenesis in vivo (**Section II**). That is, assuming *arguendo* that there were a motivation to combine the references in the manner proffered by the Examiner, the combination still does not teach or suggest the claimed invention, i.e., the combination of **VEGF and GM-CSF (Section III)**. Because the cited combination of references does not put one of ordinary

skill in the art in possession of the claimed invention, one of ordinary skill in the art would not have a reasonable expectation of success in making and using the claimed invention based on the cited combination of references. Accordingly, withdrawal of the rejection is respectfully requested.

Claims 50, 52, 55-63, 65-68, 70, 72-78, and 84 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Kaplan in view of U.S. Patent No. 5,880,090 ("Hammond") and Asahara et al. Science, 1997 ("Asahara").

The Office Action alleges that Kaplan taught methods for promoting angiogenesis in tissue surrounding a body lumen in a region of ischemic tissue by delivering an angiogenic factor to a target site. Exemplary angiogenic factors including VEGF, bFGF, aFGF, EGF, PDGF, and fragments thereof. However, the Office Action states that neither Kaplan nor Ferrara teach the combination of both VEGF and GM-CSF. The Office Action further alleges that Hammond taught administration of an agent including stem cell factor, GM-CSF, and G-CSF into a graft recipient to mobilize endothelial progenitor cells into the bloodstream. Hammond is also alleged to have taught that more than one endothelial-promoting agent including FGF, VEGF, and angiopoietin may be administered concomitantly. Hammond is also alleged to have noted that Asahara had shown that $CD34^+$ endothelial cell populations are capable of differentiating into endothelial-like cells and may participate in the repair of ischemic tissue. The Office Action states that it would have been obvious for an ordinary skilled artisan to modify the method of Kaplan by administering an agent such as SCF, GM-CSF, and G-CSF to a mammal having ischemia.

The Office Action alleges that the Rule 131 Declaration submitted by the Applicant is insufficient to antedate the Hammond reference. The Office Action states that the Declaration is insufficient and that it does not demonstrate conception of the invention prior to September 19, 1997. In continuation of the arguments presented in Applicants' previous response of May 23, 2008, Applicants respectfully disagree.

The Declaration provides data from the specific combination of VEGF and GM-CSF, as claimed. At point 8 and in Exhibit 2, Applicant demonstrates that the combination of VEGF and GM-CSF are effective in promoting angiogenesis in an accepted *in vivo* model. The corneal angiogenesis model allows for the study of the effects of potentially angiogenic factors in a

tissue that is avascular that can be observed over time without disrupting the tissue. At the same time that the inventors were performing angiogenic assays using a combination of VEGF and GM-CSF in cornea, they were also performing angiogenesis assays in ischemic animal models using GM-CSF. Moreover, they were studying the mechanism of action of GM-CSF on endothelial progenitor cells which provided an understanding of the role of GM-CSF in neovascularization that allowed them to better correlate results from multiple neovascularization models.

The Office Action states at the paragraph spanning pages 16-17:

> It is noted that nowhere in the Declaration filed on 2/17/04 under 37 CFR 1.131, including at point 8 and in Exhibit 2, is there evidence indicating or suggesting that Applicants contemplated specifically a method for inducing formation of new blood vessels **in a mammal having chronic or acute ischemia** or a method for preventing or reducing the severity of blood vessel damage **in a mammal having chronic or acute ischemia** by administereing to the mammal **an effective amount of VEGF and GM-CSF as claimed**. At point 8 as well as in Exhibit 2, Applicants simply disclose that **normal mice were pre-treated with GM-CSF**, VEGF pellets were inserted into corneas of GMCSF[sic]-pretreated mice primarily **to attract or to monitor** mobilized endothelial progenitor cells induced by GM-CSF; and not for treating any mammal having chronic or acute ischemia. [Examiner's emphasis]

Applicants respectfully submit that the Office's position regarding the Rule 131 Declaration filed on 2/17/04 is inconsistent with the application of Bussolino in separate rejections under 35 U.S.C. §103(a) (i.e., Kaplan in view of Bussolino and Ferrara in view of Bussolino). Bussolino performed rabbit corneal experiments similar to Applicants's mice corneal experiments to determine *in vivo* angiogenic activity. Likewise, Bussolino did not use animals suffering from chronic or acute ischemia. Nevertheless, the Office has concluded that such experiments would have suggested to one of skill in the art that a combination of cytokines would be useful in treating chronic or acute ischemia. In the same way that the Office has applied Bussolino, Applicants submit that it would have been apparent to one of skill in the art, that the combination of VEGF and GM-CSF would be useful in treating chronic or acute ischemia based on the results of the mice corneal experiments at point 8 and in Exhibit 2. **(Aside from this particular teaching, Applicants note that Bussolino contains other deficiencies, as described above, that preclude it from supporting any rejection for obviousness).**

The Declaration teaches that the change in EPC kinetics due to treatment with GM-CSF results in increased neovascularization. As a change in kinetics would result in a systemic effect, demonstration of an effect on neovascularization in one tissue (e.g., cornea) would result in the understanding that the same effect would be seen in neovascularization in all tissues. Specifically, page 2 of Exhibit 2 states:

> These results indicates GMCSF exerts potent stimuli on EPC kinetics and such a cytokine-induced EPC mobilization can enhance neovascularization in severe ischemia condition and de novo vascularization in avascular area.

Therefore, the Declaration demonstrates that the inventors had conceived that the effects observed in an ischemic model, as claimed, would be predictive of results that would be obtained in an avascular area, e.g., cornea. Similarly, the inventors understood that the data obtained in the corneal model, discussed at point 8 of the Declaration, would be predictive of results that would be observed in an ischemic model. Likewise, the Office's application of Bussolino indicates that one skilled in the art would recognize the significance of the data presented in the Rule 131 Declaration.

The data in the specification combined with the conclusions in the manuscript demonstrate full conception of the invention as claimed. As the invention was conceived prior to the date of the Hammond reference, it is not available for the rejection of the claims for obviousness. As the combination of the Kaplan and Asahara references is insufficient to make the claimed invention obvious, the rejection is overcome. Withdrawal of the rejection is respectfully requested.

Double Patenting Rejections

Claims 50, 55-63, 65-67 and 84 are provisionally rejected under the judicially created doctrine of double patenting over claims 3-4 and 11 of U.S. Patent No. 5,980,887. Claims 50, 52, 55-63, 65-68, 70, 72-78 and 84 are rejected on the grounds of nonstatutory obviousness-type double patenting as unpatentable over claims 1-11 of U.S. Patent No. 5,980,887 in view of Hammond and Asahara. Claims 50, 55-63, 65-67 and 84 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 49-52, 54-59, 62-65, and 68-69 of co-pending U.S. Patent Application No. 10/696,391. Claims 50, 55-63, 65-67 and 84 are provisionally rejected under the judicially created doctrine of obviousness-type

double patenting over claims 49, 58-60, and 68-70 of co-pending U.S. Patent Application No. 10/714,574.

Applicants respectfully traverse the rejections. Applicants will address the double patenting rejections of the claims upon a finding that the claims (that will be pending upon entry of the amendments presented herein) are in condition for allowance, but for the instant double patenting rejection. As the Office has not yet indicated any allowed claims, Applicants have not addressed the obviousness-type double patenting rejections.

CONCLUSION

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of all rejections and allowance of the application with claims 50, 52, 55-63, 65-68, 70, 72-78, and 84 presented herein. In advance of the issuance of a final Office Action, Applicants invite the Examiner to call the undersigned at the telephone number indicated below to schedule an interview.

Applicants submit this paper in response to the Office Action dated August 11, 2008, in the above-referenced patent application, along with a request for a two-month extension of time and the required fee based on large entity status set forth in 37 CFR §1.17. Applicants believe that no additional fee is due to consider the present amendment. Nevertheless, the Director is hereby authorized to charge or credit any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. **04-1105**, under Order No. 47624DIV2(71417).

Dated: January 12, 2009

Respectfully submitted,

By _____

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